IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:David BROWN et al.	**Confirmation No. 4047** Group Art Unit: 1615
Appl. No.	:10/736,902	Examiner: Sheikh, Humera N.
Filed	:December 17, 2003	
For	:DOSAGE FORM CONTAINING PROMETHAZINE AND ANOTHER DRUG	

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief - Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This Appeal is from the Examiner's Final Rejection of claims 1-24, 27-38 and 68-74 set forth in the Office Action mailed from the U.S. Patent and Trademark Office on November 23, 2007.

A Notice of Appeal in response to the November 23, 2007 Final Office Action was filed on February 25, 2008.

The requisite fee under 37 C.F.R. § 41.20(b)(2) for filing this Appeal Brief (for a Small Entity) is being paid concurrently herewith.

Inasmuch as this Appeal Brief is being filed within the initial two-month period prescribed by 37 C.F.R. § 41.37(a)(1), set to expire April 25, 2008, it is believed that no extension of time is required. However, the Patent and Trademark Office is authorized to charge any fee necessary for maintaining the pendency of this application, including any appeal or extension of time fees that may be necessary, to Deposit Account No. 19-0089.

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I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Sovereign Pharmaceuticals, Ltd. of Fort Worth, Texas. The corresponding assignment was recorded in the U.S. Patent and Trademark Office on April 2, 2004 at REEL 015176, FRAME 0813.

II. RELATED APPEALS AND INTERFERENCES

Appellants note that a Notice of Appeal was filed on February 19, 2008 in co-pending and commonly assigned Application No. 10/798,884, which application contains claims over which the present claims have provisionally been rejected on the ground of nonstatutory obviousness-type double patenting (see page 3, first paragraph of the Final Office Action mailed November 23, 2007). Appellants, Appellants' representative or the Assignee are not aware of any other prior and pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The status of the claims is as follows:

Claims 1-74 are pending in this application.

Claims 25, 26 and 39-67 are withdrawn from consideration.

Each of claims 1-24, 27-38 and 68-74 is indicated as rejected in the Final Office Action mailed November 23, 2007.

The rejection of each of claims 1-24, 27-38 and 68-74 is under appeal. Claims 1-24, 27-38 and 68-74 involved in the appeal are reproduced in the Claims Appendix attached hereto.

IV. STATUS OF AMENDMENTS

No Amendment has been filed subsequent to the Final Office Action mailed November 23, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Claim 1

Independent claim 1 is drawn to a pharmaceutical dosage form which comprises (a) a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof and (b) at least one second drug. The dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 2, lines 13-18 from bottom and page 27, lines 3-8 of the present specification.

B. Claim 27

Independent claim 27 is drawn to a bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug and the second layer comprising at least one second drug. The first drug is at least one of promethazine and a

pharmaceutically acceptable salt thereof and the at least one second drug is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines. The bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of the period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 3, lines 11-19 and page 29, line 6 from bottom to page 30, line 2 of the present specification.

C. Claim 68

Independent claim 68 is drawn to a pharmaceutical dosage form which comprises (a) a first drug which is an antihistamine and has a first plasma half-life and (b) at least one second drug which is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines and has a second plasma half-life. The second plasma half-life differs from the first plasma half-life by at least about 3 hours. Further, the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 6, lines 13-21 and page 35, lines 9-16 from bottom of the present specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The broad issues under consideration are:

1. Whether claims 1-24, 27-38 and 68-74 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA") in view of Findlay et al., U.S. Patent No. 4,650,807 (hereafter "FINDLAY") and in particular, whether the disclosure of FANARA in view of FINDLAY is sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 1-24, 27-38 and 68-74.

2. Whether claims 1-24, 27-38 and 68-74 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of Paradissis et al., U.S. Patent No. 5,445,829 (hereafter "PARADISSIS") and in particular, whether the disclosure of FANARA in view of PARADISSIS is sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 1-24, 27-38 and 68-74.

Appellants further note that the Examiner has provisionally rejected the above claims under the nonstatutory doctrine of obviousness-type double patenting as allegedly being unpatentable over certain claims of co-pending Application Nos. 10/798,884, 10/910,806, 10/939,351, 11/012,267, 11/115,321, 11/102,725, 11/102,726 and 11/115,293. Appellants will address these provisional rejections once the Board has rendered a decision on the above issues 1. and 2.

VII. ARGUMENTS

A. Citation of Authority

Obviousness

The appropriate starting point for a determination of obviousness is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 466 (1966):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

The test of obviousness *vel non* is statutory and requires a comparison of the claimed subject matter as a whole with the prior art to which the subject matter pertains. *In re Brouwer*, 77 F.3d, 422, 37 U.S.P.Q. 2d 1663 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 37 U.S.P.Q. 2d 1127 (Fed. Cir. 1995).

Often, it will be necessary to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. This analysis should be made explicit. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741. "A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be

important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id*, at 1741.

"If the Examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned." *In re Rijckaert*, 9 F.3d, 1532, 28 U.S.P.Q.2d, 1956 (Fed. Cir. 1993), citing *In re Fine*, 837 F.2d 1071, 1074,5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

B. Claims 1-24, 27-38 and 68-74 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Unpatentable Over FANARA in View of FINDLAY

1. Summary of Rejection

The rejection essentially alleges that FANARA discloses, at least inherently, all of the elements of the rejected claims with the exception of promethazine and chlorpheniramine as antihistamines and guaifenesin as antitussive-expectorant (see page 13, second paragraph of Final Office Action mailed November 23, 2007).

In particular, regarding the recitation of "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug" in the present independent claims the Examiner appears to take the position that FANARA discloses this element inherently, alleging that FANARA "explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic

profiles. Thus, the Fanara reference teaches an objective similar to that claimed by Applicant". Page 12, second paragraph of the Final Office Action.

Regarding the plasma half-lives recited in the present claims, the rejection alleges that "the Fanara reference teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant." Page 12, third paragraph of the Final Office Action.

With respect to FINDLAY, the rejection alleges that this document teaches antihistaminic compositions which can be in the form of tablets and also teaches pheniramines and promethazine as suitable antihistamines. The rejection further asserts that FINDLAY teaches that the active compound may be formulated with a sympathomimetic agent such as decongestants, an antitussive, an analgesic, anti-inflammatory or an antitussive expectorant, and that it would allegedly have been obvious to one of ordinary skill in the art to incorporate the suitable antihistamines and expectorants allegedly taught by FINDLAY within the formulations of FANARA (page 13, 3rd and 4th paragraphs of Final Office Action).

2. Response

a. FANARA in View of FINDLAY Fails to Render Obvious Independent Claim 1

(i) FANARA

Appellants respectfully submit that the Examiner's conclusions with respect to FANARA are based on hindsight. In particular, FANARA is concerned primarily with pharmaceutical compositions for the controlled release of active substances (see, e.g., title and col. 1, first paragraph of FANARA), not with the administration of different

active substances in a single dosage form and for this reason alone, one of ordinary skill in the art has no reason to consult FANARA for guidance in the latter respect.

The passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states (emphasis added):

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

The Examiner appears to take the position that in view of the above passage one of ordinary skill in the art allegedly would have an apparent reason to provide a dosage form which comprises two different active substances, one released immediately after administration and the other one released gradually and regularly after administration, and releases these two active substances in such a manner that the plasma concentration of one active substance is within a therapeutic range over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of the other active substance is within a therapeutic range.

In this regard, it is noted that the above passage makes reference to active substances which have "very different pharmacokinetic profiles" and can be administered by means of the immediate/controlled release formulations of FANARA. However, FANARA does not explain what exactly is to be understood by the phrase "very different

pharmacokinetic profiles". In this regard, it is pointed out that the term "pharmacokinetic profile" encompasses a wide range of properties of a drug.

For example, according to

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

(see EVIDENCE APPENDIX) the term "pharmacokinetic profile" is defined as "[t]he characteristics of a drug that determine its absorption, distribution and elimination in the body". Appellants are unable to see why the fact that FANARA mentions that the immediate/controlled release combinations set forth therein make it possible to obtain combined therapeutic effects by means of two active substances which have very different absorption, distribution and elimination characteristics in the body allegedly renders it obvious to one of ordinary skill in the art to use an immediate/controlled release combination for providing plasma concentrations in a therapeutic range of these two active substances in such a way that the therapeutically effective period of one drug overlaps at least about 70 % of the therapeutically effective period of the other drug.

Appellants further are unable to find any other statements in FANARA which would support a conclusion that FANARA renders it obvious to one of ordinary skill in the art to provide the subject matter of present claim 1.

In this regard, it additionally is pointed out that the above-cited passage of FANARA must be considered and assessed in the context of the entire disclosure of FANARA.

For example, in lines 15-27 of col. 3, the inventors of FANARA make it clear that their contribution to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two different active substances but rather that

their invention consists in the provision of a new matrix composition for the controlled release part of corresponding dosage forms (and, primarily, for dosage forms which consist of only a single, controlled release composition), which matrix composition has certain advantages.

Specifically, the inventors of FANARA acknowledge that "orally administrable solid pharmaceutical compositions combining, in a single unit, a portion exhibiting immediate release and a portion exhibiting delayed release have been described" but allege that these compositions are difficult to make and are not available in the desired form for each and every active substance. It further is stated in FANARA that the controlled release matrix compositions disclosed therein "do not require excessive quantities of matrix excipients and allow regular and continuous release of active substances over periods of at least 12 hours."

Accordingly, one of ordinary skill in the art will understand that FANARA neither teaches nor suggests combined immediate/controlled release dosage forms which are different from the known dosage forms in any respect other than the composition of the matrix for the controlled release portion thereof.

Further, FANARA does not at all convey the impression that immediate/controlled release dosage forms are advantageous or even only suitable for each and every combination of two active substances. For example, in the passage from col. 5, line 39 to col. 6, line 26 FANARA states (emphasis added):

> According to a specific embodiment of the invention, the controlled-release pharmaceutical compositions according to the invention are used in combination with one or more pharmaceutical compositions allowing immediate release of active substances. When these two types of compositions are present in the same unit, this makes it possible to obtain, in a single administration, both the immediate

release of a first active substance and the prolonged release of the same or of a second active substance.

Accordingly, the present invention also relates to pharmaceutical compositions which can be administered orally, comprising

A. at least one layer comprising an active substance and excipients which allow immediate release of the said active substance after administration, and
B. at least a second layer which allows the controlled release of the same or of a second active substance, comprising the said same or second active substance, at least one matrix-type excipient and at least one alkalinizing agent.

[...]

Such combined pharmaceutical compositions can be prepared according to various methods known to persons skilled in the art.

More particularly, these combined pharmaceutical compositions may be provided in the form of a tablet in which at least one layer A is stuck to at least one layer B.

[...]

The multilayer tablets are particularly well suited to cases of combinations of active substances for which very specific beneficial therapeutic effects have recently been obtained, for example, pseudoephedrine/cetirizine, hydrocodone/acetaminophen, immediate release hydrocodone/prolonged release hydrocodone.

The embodiments referred to by FANARA in the last paragraph of the above passage are illustrated in Example 4 (double-layer tablet containing controlled-release pseudoephedrine and immediate release cetirizine) and Example 7 (double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer).

The fact that FANARA mentions only a few very specific examples of combinations of active substances for which the immediate/controlled release dosage forms (multilayer tablets) mentioned therein may be "particularly well suited" rather than pointing out that these multilayer tablets are advantageous with respect to the administration of any combination of two active substances is a clear indication that the inventors of FANARA were not at all concerned about the overlap of the periods of

therapeutic effectiveness of these active substances. This is further supported by, e.g., Table 10 in col. 10 of FANARA which compares the time-dependent release of the two active substances (pseudoephedrine and cetrizine) in the double-layer tablet of Example 4 but fails to provide any information whatsoever regarding the duration of action of these two active substances, let alone regarding the overlap in the periods of therapeutic effectiveness thereof.

At any rate, there is not even a single passage in FANARA wherein the duration of action of any active substance is addressed. Whenever combinations of active substances are mentioned in FANARA these combinations are to be contained in immediate release/controlled release dosage forms, i.e., dosage forms which are designed for the sole purpose of providing different release rates and/or release periods of the active substances, i.e., without any concern regarding the time and duration of action of one active substance in relation to the time and duration of action of the other active substance. This fact alone should make it apparent that FANARA is unable to render obvious the subject matter of claim 1, i.e., a claim which addresses, in terms of plasma concentrations within a therapeutic range, the relationship (overlap) between the time and duration of action (the period of therapeutic effectiveness) of one specific drug (promethazine) and the time and duration of action of another (second) drug which is comprised in the same dosage form.

Appellants further point out that the Examiner apparently was unable to cite any document which in combination with FANARA could be considered to render it obvious to one of ordinary skill in the art to use the immediate/controlled release dosage forms set forth in FANARA for providing a plasma concentration within a therapeutic range of one

drug over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of any other drug (and specifically, promethazine) is in the therapeutic range.

In other words, even if one were to agree, *arguendo*, with the Examiner that FANARA "teaches an objective similar to that being claimed by Applicant" Applicants are unable to see that this renders obvious the recitation "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug" in, e.g., present claim 1, let alone in combination with the fact that the first drug is promethazine and/or a pharmaceutically acceptable salt thereof, i.e., a drug which is not even mentioned in FANARA.

(ii) FINDLAY

Regarding FINDLAY, Applicants respectfully submit that contrary to what is alleged in the third paragraph of page 13 of the Final Office Action, this document does not teach that suitable antihistamines for the composition disclosed therein include pheniramines and promethazine. On the contrary, in col. 1, lines 27-39, FINDLAY states (emphases added):

> The antihistamines now in use, eg. diphenhydramine, pheniramines, pyrilamine, promethazine and triprolidine, exhibit varying degrees of anticholinergic activity. Such activity causes dryness of mouth, blurred vision and tachycardia and is generally regarded as undesirable.
>
> A novel compound having potent antihistamine activity which is substantially free from sedative effects, and which has little or no anticholinergic effect has now been discovered.

Accordingly this invention provides the compound of formula (I), which is named (E)-3-{6-[3-Pyrrolidino-1-(4-tolyl)prop-1E-enyl]-2-pyridyl}acrylic acid.

Accordingly, even if one were to assume, *arguendo*, that one or ordinary skill in the art would be motivated to combine the teachings of FANARA and FINDLAY, the latter document would teach away from including promethazine as an antihistamine in a composition disclosed by FANARA. This is yet another reason why even a combination of the teachings of FANARA and FINDLAY fails to render obvious the subject matter of any of the present claims.

At any rate, FINDLAY is unable to cure the deficiencies of FANARA set forth above and in particular, is unable to render it obvious to one of ordinary skill in the art to provide a dosage form which comprises promethazine and/or a pharmaceutically acceptable salt thereof (or any other drug) and a second drug and provides a period of therapeutic effectiveness of the second drug which overlaps (is coextensive with) at least about 70 % of the period of therapeutic effectiveness of the promethazine and/or a pharmaceutically acceptable salt thereof.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of independent claim 1 (and any of the claims dependent therefrom) over FANARA in view of FINDLAY.

b. FANARA in View of FINDLAY Fails to Render Obvious Independent Claim 27

Claim 27 has in common with independent claim 1, *inter alia,* that it also recites a pharmaceutical dosage form, i.e., a bi-layered tablet, which comprises promethazine

and/or a pharmaceutically acceptable salt thereof and at least one second drug (in particular, a drug selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % of the period over which the plasma concentration of the first drug is within a therapeutic range.

As set forth in detail above in section VII.B.2.a. with respect to independent claim 1, FANARA in view of FINDLAY *inter alia* fails to render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which releases any two different drugs in a way such that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70 %. Moreover, it is pointed out again that although FANARA mentions several examples of antihistamines in the last paragraph of column 4 thereof, it fails to mention promethazine, whereas FINDLAY, for the reasons also detailed above in section VII.B.2.a., even teaches away from employing promethazine in pharmaceutical compositions by pointing out that this compound has several undesirable side effects.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of independent claim 27 (and any of the claims dependent therefrom) over FANARA in view of FINDLAY as well.

c. FANARA in View of FINDLAY Fails to Render Obvious Independent Claim 68

Claim 68 has in common with independent claim 1, *inter alia,* that it also recites a pharmaceutical dosage form which comprises a an antihistamine as first drug and at least

one second drug (in particular, a drug selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % of the period over which the plasma concentration of the first drug is within a therapeutic range. Compared to claim 1, claim 68 additionally recites that the plasma half-lives of the first and second drugs differ by at least about 3 hours.

As set forth in detail above in section VII.B.2.a. with respect to independent claim 1, FANARA in view of FINDLAY fails to *inter alia* render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which releases any two different drugs in such a way that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70 %.

Additionally, neither FANARA nor FINDLAY mentions or addresses any plasma half-lives, let alone the difference in the plasma half-lives of two drugs which are comprised in the same dosage form, which is yet another reason why FANARA in view of FINDLAY is unable to render obvious the subject matter of claim 68.

In this regard, Appellants respectfully disagree with the Examiner with respect to the assertion that FANARA "teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant."

Specifically, claim 68 does not recite the specific plasma half-lives of any two drugs which are comprised in a single dosage form but the difference in the plasma half-lives of these two drugs of which one is an antihistamine and the other is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines. Appellants point out that the Examiner has failed to provide any (written

or other) evidence that two drugs whose combination in a single dosage form is taught or suggested by FANARA in view of FINDLAY have plasma half-lives which differ by at least about 3 hours (as recited in claim 68).

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness also with respect to the subject matter of independent claim 68 (and any of the claims dependent therefrom) over FANARA in view of FINDLAY.

d. FANARA in View of FINDLAY Fails to Render Obvious Dependent Claims 12-14

Claims 12-14 depend, directly or indirectly, from independent claim 1 and recite that in the dosage form recited in the latter claim the plasma half-life of the at least second drug is shorter than the plasma half-life of the first drug (promethazine and/or a pharmaceutically acceptable salt thereof) by at least about 3, 4 or 6 hours respectively.

As set forth above with respect to independent claim 68, neither FANARA nor FINDLAY mentions or addresses any plasma half-lives, let alone the difference in the plasma half-lives of two drugs which are comprised in the same dosage form.

Moreover, there is nothing of record which would support the allegation that two drugs whose combination in a single dosage form is taught or suggested by FANARA in view of FINDLAY have plasma half-lives which differ by at least about 3 hours.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter recited in dependent claims 12-14 over FANARA in view of FINDLAY.

C. Claims 1-24, 27-38 and 68-74 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Unpatentable Over FANARA in View of PARADISSIS

1. Summary of Rejection

The rejection with respect to FANARA is the same as in the case of the rejection of the same claims over FANARA in view of FINDLAY (see section VII.B.1. above). Specifically, the rejection essentially alleges that FANARA discloses, at least inherently, all of the elements of the rejected claims with the exception of promethazine and chlorpheniramine as antihistamines and guaifenesin as expectorant (see page 17, second paragraph of Final Office Action mailed November 23, 2007).

Regarding PARADISSIS the rejection alleges that this document teaches extended release pharmaceutical compositions (preferably in the form of a tablet) containing both an immediate release formulation and an extended release formulation and that the compositions include pharmaceutically active compounds, such as antihistamines (suitable examples whereof allegedly include chlorpheniramine maleate and promethazine), antitussives, expectorants and decongestants (suitable antitussive-expectorants allegedly include guaifenesin). The rejection further asserts that it would allegedly have been obvious for one of ordinary skill in the art "to incorporate the suitable antihistamines and antitussive-expectorants taught by Paradissis et al. within the formulations of Fanara et al." Page 17, last paragraph of Final Office Action.

2. Response

a. FANARA in View of PARADISSIS Fails to Render Obvious Independent Claim 1

(i) FANARA

Appellants respectfully submit that the Examiner's conclusions with respect to FANARA are based on hindsight. In particular, FANARA is concerned primarily with pharmaceutical compositions for the controlled release of active substances (see, e.g., title and col. 1, first paragraph of FANARA), not with the administration of different active substances in a single dosage form and for this reason alone, one of ordinary skill in the art has no reason to consult FANARA for guidance in the latter respect.

The passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states (emphasis added):

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

The Examiner appears to take the position that in view of the above passage one of ordinary skill in the art allegedly would have an apparent reason to provide a dosage form which comprises two different active substances, one released immediately after administration and the other one released gradually and regularly after administration, and releases these two active substances in such a manner that the plasma concentration of one active substance is within a therapeutic range over a period which is coextensive

with at least about 70 % of the period over which the plasma concentration of the other active substance is within a therapeutic range.

In this regard, it is noted that the above passage makes reference to active substances which have "very different pharmacokinetic profiles" and can be administered by means of the immediate/controlled release formulations of FANARA. However, FANARA does not explain what exactly is to be understood by the phrase "very different pharmacokinetic profiles". In this regard, it is pointed out that the term "pharmacokinetic profile" encompasses a wide range of properties of a drug.

For example, according to

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(see EVIDENCE APPENDIX) the term "pharmacokinetic profile" is defined as "[t]he characteristics of a drug that determine its absorption, distribution and elimination in the body". Appellants are unable to see why the fact that FANARA mentions that the immediate/controlled release combinations set forth therein make it possible to obtain combined therapeutic effects by means of two active substances which have very different absorption, distribution and elimination characteristics in the body allegedly renders it obvious to one of ordinary skill in the art to use an immediate/controlled release combination for providing plasma concentrations in a therapeutic range of these two active substances in such a way that the therapeutically effective period of one drug overlaps at least about 70 % of the therapeutically effective period of the other drug.

Appellants further are unable to find any other statements in FANARA which would support a conclusion that FANARA renders it obvious to one of ordinary skill in the art to provide the subject matter of present claim 1.

In this regard, it additionally is pointed out that the above-cited passage of FANARA must be considered and assessed in the context of the entire disclosure of FANARA.

For example, in lines 15-27 of col. 3, the inventors of FANARA make it clear that their contribution to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two different active substances but rather that their invention consists in the provision of a new matrix composition for the controlled release part of corresponding dosage forms (and, primarily, for dosage forms which consist of only a single, controlled release composition), which matrix composition has certain advantages.

Specifically, the inventors of FANARA acknowledge that "orally administrable solid pharmaceutical compositions combining, in a single unit, a portion exhibiting immediate release and a portion exhibiting delayed release have been described" but allege that these compositions are difficult to make and are not available in the desired form for each and every active substance. It further is stated in FANARA that the controlled release matrix compositions disclosed therein "do not require excessive quantities of matrix excipients and allow regular and continuous release of active substances over periods of at least 12 hours."

Accordingly, one of ordinary skill in the art will understand that FANARA neither teaches nor suggests combined immediate/controlled release dosage forms which are different from the known dosage forms in any respect other than the composition of the matrix for the controlled release portion thereof.

Further, FANARA does not at all convey the impression that immediate/controlled release dosage forms are advantageous or even only suitable for each and every combination of two active substances. For example, in the passage from col. 5, line 39 to col. 6, line 26 FANARA states (emphasis added):

> According to a specific embodiment of the invention, the controlled-release pharmaceutical compositions according to the invention are used in combination with one or more pharmaceutical compositions allowing immediate release of active substances. When these two types of compositions are present in the same unit, this makes it possible to obtain, in a single administration, both the immediate release of a first active substance and the prolonged release of the same or of a second active substance.
>
> Accordingly, the present invention also relates to pharmaceutical compositions which can be administered orally, comprising
>
> C. at least one layer comprising an active substance and excipients which allow immediate release of the said active substance after administration, and
>
> D. at least a second layer which allows the controlled release of the same or of a second active substance, comprising the said same or second active substance, at least one matrix-type excipient and at least one alkalinizing agent.
>
> [...]
>
> Such combined pharmaceutical compositions can be prepared according to various methods known to persons skilled in the art.
>
> More particularly, these combined pharmaceutical compositions may be provided in the form of a tablet in which at least one layer A is stuck to at least one layer B.
>
> [...]
>
> The multilayer tablets are particularly well suited to cases of combinations of active substances for which very specific beneficial therapeutic effects have recently been obtained, for example, pseudoephedrine/cetirizine, hydrocodone/acetaminophen, immediate release hydrocodone/prolonged release hydrocodone.

The embodiments referred to by FANARA in the last paragraph of the above passage are illustrated in Example 4 (double-layer tablet containing controlled-release pseudoephedrine and immediate release cetirizine) and Example 7 (double-layer tablet

containing hydrocodone in both a controlled-release layer and an immediate release layer).

The fact that FANARA mentions only a few very specific examples of combinations of active substances for which the immediate/controlled release dosage forms (multilayer tablets) mentioned therein may be "particularly well suited" rather than pointing out that these multilayer tablets are advantageous with respect to the administration of any combination of two active substances is a clear indication that the inventors of FANARA were not at all concerned about the overlap of the periods of therapeutic effectiveness of these active substances. This is further supported by, e.g., Table 10 in col. 10 of FANARA which compares the time-dependent release of the two active substances (pseudoephedrine and cetrizine) in the double-layer tablet of Example 4 but fails to provide any information whatsoever regarding the duration of action of these two active substances, let alone regarding the overlap in the periods of therapeutic effectiveness thereof.

At any rate, there is not even a single passage in FANARA wherein the duration of action of any active substance is addressed. Whenever combinations of active substances are mentioned in FANARA these combinations are to be contained in immediate release/controlled release dosage forms, i.e., dosage forms which are designed for the sole purpose of providing different release rates and/or release periods of the active substances, i.e., without any concern regarding the time and duration of action of one active substance in relation to the time and duration of action of the other active substance. This fact alone should make it apparent that FANARA is unable to render obvious the subject matter of claim 1, i.e., a claim which addresses, in terms of plasma

concentrations within a therapeutic range, the relationship (overlap) between the time and duration of action (the period of therapeutic effectiveness) of one specific drug (promethazine) and the time and duration of action of another (second) drug which is comprised in the same dosage form.

Appellants further point out that the Examiner apparently was unable to cite any document which in combination with FANARA could be considered to render it obvious to one of ordinary skill in the art to use the immediate/controlled release dosage forms set forth in FANARA for providing a plasma concentration within a therapeutic range of one drug over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of any other drug (and specifically, promethazine) is in the therapeutic range.

In other words, even if one were to agree, *arguendo*, with the Examiner that FANARA "teaches an objective similar to that being claimed by Applicant" Applicants are unable to see that this renders obvious the recitation "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug" in, e.g., present claim 1, let alone in combination with the fact that the first drug is promethazine and/or a pharmaceutically acceptable salt thereof, i.e., a drug which is not even mentioned in FANARA.

(ii) PARADISSIS

PARADISSIS is unable to cure the deficiencies of FANARA set forth above and in particular, is unable to render it obvious to one of ordinary skill in the art to provide a dosage form which comprises (any) two different drugs and releases them in such a way that the period of therapeutic effectiveness of one drug overlaps at least about 70 % of the period of therapeutic effectiveness of the other drug. This appears to be conceded, at least implicitly, in the Final Office Action mailed November 23, 2007.

At any rate, PARADISSIS, like FANARA, is concerned primarily with extended (controlled) release formulations as such and makes it clear that combinations of these extended release formulations with immediate release formulations are merely optional (see, e.g., title and col. 1, lines 15-26 of PARADISSIS). This fact alone is a clear indication that PARADISSIS is not concerned at all with any overlap in the periods of therapeutic effectiveness of two drugs which are comprised in the same dosage form.

Additionally, PARADISSIS fails to provide any apparent reason for one of ordinary skill in the art to employ promethazine, i.e., a drug which is mentioned in col. 4, lines 31-64 of PARADISSIS among several dozens of exemplary substances which can be incorporated in the pharmaceutical formulations disclosed therein and is not even included in the list of preferred drugs in the paragraph bridging columns 4 and 5 of this document, let alone in combination with any of the other exemplary drugs mentioned in PARADISSIS.

In this regard, it further is pointed out that the list of preferred drugs provided by PARADISSIS includes an antihistamine, i.e., chlorpheniramine maleate. Accordingly, since promethazine and chlorpheniramine are both antihistamines PARADISSIS provides

a disincentive rather than a motivation to use promethazine (i.e., not chlorpheniramine) instead of any of the antihistamines specifically mentioned in the last paragraph of col. 4 of FANARA if one were to assume, merely for the sake of argument, that one of ordinary skill in the art would want to replace the antihistamines mentioned in FANARA by a different antihistamine.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of independent claim 1 (and any of the claims dependent therefrom) over FANARA in view of PARADISSIS.

b. FANARA in View of PARADISSIS Fails to Render Obvious Independent Claim 27

Claim 27 has in common with independent claim 1, *inter alia,* that it also recites a pharmaceutical dosage form, i.e., a bi-layered tablet, which comprises promethazine and/or a pharmaceutically acceptable salt thereof and at least one second drug (in particular, a drug selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % of the period over which the plasma concentration of the first drug is within a therapeutic range.

As set forth in detail above in section VII.C.2.a. with respect to independent claim 1, FANARA in view of PARADISSIS *inter alia* fails to render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which releases any two different drugs in such a way that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about

70 %. Moreover, it is pointed out again that although FANARA mentions several examples of antihistamines in the last paragraph of column 4 thereof, it fails to mention promethazine, whereas PARADISSIS, for the reasons also detailed above in section VII.B.2.a., provides a disincentive rather than an apparent reason for one of ordinary skill in the art to employ promethazine in pharmaceutical compositions according to FANARA by clearly favoring chlorpheniramine (maleate) as antihistamine.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of independent claim 27 (and any of the claims dependent therefrom) over FANARA in view of PARADISSIS as well.

c. FANARA in View of PARADISSIS Fails to Render Obvious Independent Claim 68

Claim 68 has in common with independent claim 1, *inter alia,* that it also recites a pharmaceutical dosage form which comprises a an antihistamine as first drug and at least one second drug (in particular, a drug selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % of the period over which the plasma concentration of the first drug is within a therapeutic range. Compared to claim 1, claim 68 additionally recites that the plasma half-lives of the first and second drugs differ by at least about 3 hours.

As set forth in detail above in section VII.C.2.a. with respect to independent claim 1, FANARA in view of PARADISSIS fails to *inter alia* render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which

releases any two different drugs in such a way that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70 %.

Additionally, neither FANARA nor PARADISSIS mentions or addresses any plasma half-lives, let alone the difference in the plasma half-lives of two drugs which are comprised in the same dosage form, which is yet another reason why FANARA in view of PARADISSIS is unable to render obvious the subject matter of claim 68.

In this regard, Appellants respectfully disagree with the Examiner with respect to the assertion that FANARA "teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant."

Specifically, claim 68 does not recite the specific plasma half-lives of any two drugs which are comprised in a single dosage form but the difference in the plasma half-lives of these two drugs of which one is an antihistamine and the other is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines. Appellants point out that the Examiner has failed to provide any (written or other) evidence that two drugs whose combination in a single dosage form is taught or suggested by FANARA in view of PARADISSIS have plasma half-lives which differ by at least about 3 hours (as recited in claim 68).

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness also with respect to the subject matter of independent claim 68 (and any of the claims dependent therefrom) over FANARA in view of PARADISSIS.

d. FANARA in View of PARADISSIS Fails to Render Obvious Dependent Claims 12-14

Claims 12-14 depend, directly or indirectly, from independent claim 1 and recite that in the dosage form recited in the latter claim the plasma half-life of the at least second drug is shorter than the plasma half-life of the first drug (promethazine and/or a pharmaceutically acceptable salt thereof) by at least about 3, 4 or 6 hours respectively.

As set forth above with respect to independent claim 68, neither FANARA nor PARADISSIS mentions or addresses any plasma half-lives, let alone the difference in the plasma half-lives of two drugs which are comprised in the same dosage form.

Moreover, there is nothing of record which would support the allegation that two drugs whose combination in a single dosage form is taught or suggested by FANARA in view of PARADISSIS have plasma half-lives which differ by at least about 3 hours.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter recited in dependent claims 12-14 over FANARA in view of PARADISSIS.

VIII. CONCLUSION

Appellants respectfully submit that, for at least all of the foregoing reasons the Examiner has failed to establish a *prima facie* case of obviousness of rejected claims 1-24, 27-38 and 68-74, which is a prerequisite for maintaining a rejection under 35 U.S.C. § 103. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
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CLAIMS APPENDIX

1. A pharmaceutical dosage form which comprises (a) a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof and (b) at least one second drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

2. The dosage form of claim 1, wherein the at least one second drug is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines.

3. The dosage form of claim 2, wherein the first drug comprises promethazine hydrochloride.

4. The dosage form of claim 1, wherein the at least one second drug comprises an antitussive.

5. The dosage form of claim 4, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone, dextromethorphan and pharmaceutically acceptable salts thereof.

6. The dosage form of claim 1, wherein the at least one second drug comprises a decongestant.

7. The dosage form of claim 6, wherein the second drug comprises at least one of phenylepherine, pseudoephedrine and pharmaceutically acceptable salts thereof.

8. The dosage form of claim 1, wherein the at least one second drug comprises an antihistamine.

9. The dosage form of claim 8, wherein the antihistamine comprises at least one of chlorpheniramine and pharmaceutically acceptable salts thereof.

10. The dosage form of claim 1, wherein the at least one second drug comprises an expectorant.

11. The dosage form of claim 10, wherein the expectorant comprises guaifenesin.

12. The dosage form of claim 2, wherein a plasma half-life of the at least one second drug is shorter than a plasma half-life of the first drug by at least about 3 hours.

13. The dosage form of claim 1, wherein a plasma half-life of the at least one second drug is shorter than the plasma half-life of the first drug by at least about 4 hours.

14. The dosage form of claim 12, wherein the plasma half-life of the at least one second drug is shorter than the plasma half-life of the first drug by at least about 6 hours.

15. The dosage form of claim 1, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

16. The dosage form of claim 12, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within the therapeutic range of the first drug.

17. The dosage form of claim 2, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 95 % of the period of a plasma concentration within the therapeutic range of the first drug.

18. The dosage form of claim 1, wherein the dosage form comprises a tablet.

19. The dosage form of claim 18, wherein the tablet has at least two layers.

20. The dosage form of claim 19, wherein the tablet is a bi-layered tablet.

21. The dosage form of claim 18, wherein the tablet comprises a matrix which comprises the first drug and has dispersed therein particles which comprise the at least one second drug.

22. The dosage form of claim 21, wherein the matrix has dispersed therein particles which comprise a second drug and a third drug.

23. The dosage form of claim 21, wherein the matrix has dispersed therein particles which comprise a second drug, a third drug and a fourth drug.

24. The dosage form of claim 21, wherein the matrix provides an immediate release of the first drug and the particles provide a controlled release of the at least one second drug.

27. A bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof, and the second layer comprising at least one second drug which is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

28. The bi-layered tablet of claim 27, wherein the second layer comprises at least one of phenylepherine, pseudoephedrine, chlorpeniramine and pharmaceutically acceptable salts thereof.

29. The bi-layered tablet of claim 28, wherein the first layer comprises promethazine hydrochloride and the second layer comprises at least two of phenylepherine, pseudoephedrine, chlorpeniramine and pharmaceutically acceptable salts thereof.

30. The bi-layered tablet of claim 27, wherein the first layer comprises only promethazine or a pharmaceutically acceptable salt thereof as an active ingredient.

31. The bi-layered tablet of claim 29, wherein the first layer comprises only promethazine hydrochloride as an active ingredient.

32. The bi-layered tablet of claim 30, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

33. The bi-layered tablet of claim 31, wherein the period of a plasma concentration within a therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within a therapeutic range of the first drug.

34. The bi-layered tablet of claim 30, wherein the first layer is an immediate release layer.

35. The bi-layered tablet of claim 27, wherein the second layer is a controlled release layer.

36. The bi-layered tablet of claim 34, wherein the first layer contains from about 0.1 mg to about 90 mg of promethazine hydrochloride.

37. The bi-layered tablet of claim 36, wherein the first layer contains from about 25 mg to about 50 mg of promethazine hydrochloride.

38. The bi-layered tablet of claim 36, wherein the second layer is a controlled release layer and contains at least one of (i) from about 0.1 mg to about 16 mg of chlorpheniramine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of chlorpheniramine; (ii) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; and (iii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine.

68. A pharmaceutical dosage form which comprises (a) a first drug which is an antihistamine and has a first plasma half-life and (b) at least one second drug which is

selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines and has a second plasma half-life which differs from the first plasma half-life by at least about 3 hours, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

69. The dosage form of claim 68, wherein the first plasma half-life is longer by at least about 4 hours than the plasma half-life of the at least one second drug.

70. The dosage form of claim 69, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period over which the dosage form provides a plasma concentration within the therapeutic range of the first drug.

71. The dosage form of claim 68, wherein the dosage form comprises a bi-layered tablet.

72. The dosage form of claim 70, wherein the first plasma half-life is at least about 8 hours.

73. The dosage form of claim 68, wherein the dosage form is associated with instructions to administer the dosage form three or fewer times per day.

74. The dosage form of claim 71, wherein the dosage form is associated with instructions to administer the dosage form three or fewer times per day.

EVIDENCE APPENDIX

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

downloaded from the Internet on July 5, 2007 and submitted with Response filed August 31, 2007

RELATED PROCEEDINGS APPENDIX

None.

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

Glossary

β-DYSTROGLYCAN The α- and β-dystroglycans are the laminin-binding components of the dystrophin–glycoprotein complex, which provides a linkage between the subsarcolemmal cytoskeleton and the extracellular matrix.

ACETYLCHOLINE A neurotransmitter ($C_7H_{17}NO_3$) that is released at autonomic synapses and neuromuscular junctions. It is active in the transmission of nerve impulses and is formed enzymatically in tissues from choline.

AMINOGLYCOSIDES A group of antibiotics (such as gentamicin) that inhibit bacterial protein synthesis and are particularly active against Gram-negative bacteria.

CYTOTOXICITY The properties of a virus, transgene, vector, compound or molecule that are toxic for cells.

CpG ISLAND Genomic regions that are rich in the CpG pattern, are resistant to methylation and are often associated with promoter activity.

DEPENDOVIRUS A single-stranded DNA virus from the family parvoviridae (subfamily parvovirinae), which is dependent on a co-infection with helper adenoviruses or herpes viruses for efficient replication.

DYSTROBREVINS The components of the dystrophin–glycoprotein complex that bind to syntrophin and (indirectly) to the C-terminal of dystrophin. Dystrobrevin-α recruits signalling proteins, such as neuronal nitric oxide synthase.

ELECTROPORATION The application of an electric current to the plasma membrane of a cell, to temporarily open pores or channels through which DNA might pass.

EPISOMES DNA that can replicate autonomously in the cytoplasm of host cells.

EXTRACELLULAR MATRIX In muscle, this is a thin layer (basal lamina) that contains collagen, elastin and fibronectin, which surrounds each muscle fibre. This might act as a semipermeable filter or a selective cellular barrier and is important in regeneration after damage.

F-ACTIN A protein that is involved in the contractile apparatus and the maintenance of the cytoskeleton of myofibres.

HEK-293 CELLS Host cells that generate viral particles following transfection with the rAAV plasmid and the helper plasmid.

IMMUNOGENICITY The properties of a virus, transgene, vector, compound or molecule that provoke an immune response.

MICROBUBBLES Encapsulated gas microbubbles that can be used as drug or gene carriers, which are able to penetrate into the smallest membranes. When exposed to sufficiently high-amplitude ultrasound, the microbubbles rupture and release the drugs and genes that are contained in their encapsulating layer.

MYOBLAST TRANSPLANTATION The implantation of exogenous muscle-progenitor cells into muscle to generate new myofibres or to support existing myofibres.

NEO-ANTIGEN A foreign (transgene) product that is able to stimulate an immune response.

PHARMACOKINETIC PROFILE The characteristics of a drug that determine its absorption, distribution and elimination in the body.

PRE-mRNA SPLICING The removal of introns from the precursor mRNA molecule; the remaining exons are spliced together.

PRESSURIZED ISOLATED-LIMB PERFUSION The introduction of therapeutic agents under pressure in a limb after isolation of the blood circulation by clamping.

PRIMARY MUSCLE-CELL CULTURES Cells that are taken into culture directly from a tissue biopsy. In contrast to cell lines that only contain immortalized cells, these

cultures contain heterogeneous cell populations.

RNaseH Ribonuclease H. An enzyme that cleaves RNA/DNA complexes.

SARCOLEMMA The membrane that encloses a striated muscle fibre.

SPECTRIN A large contractile submembrane protein that, similar to dystrophin, contains an actin-binding domain and a long repeat domain.

SPLICEOSOMAL COMPLEX A large dynamic complex that consists of small nuclear RNA molecules and protein components. It mediates the two catalytic steps of the splicing reaction: the excision of introns from the pre-mRNA and the ligation of the two exon termini.

SYNTROPHINS Peripheral membrane proteins that bind to the C-terminal of dystrophin, which might have a role in the process of synaptogenesis.

TRANSDUCTION The transfer of genetic material into a cell using a viral vector.

TRANSFECTION The transfer of exogenous DNA into a cell.